

What is claimed is:

1. A method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine to the subject.

5 2. The method according to claim 1, wherein the administration of the cyclooxygenase-2 selective inhibitor or prodrug thereof and the reboxetine together comprises an effective method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder.

10 3. The method according to claim 1, wherein the reboxetine is provided as a racemic mixture thereof.

15 4. The method according to claim 1, wherein the reboxetine is an R isomer thereof.

5. The method according to claim 1, wherein the reboxetine is an S isomer thereof.

20 6. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-2 IC₅₀ of less than about 0.2 μmol/L.

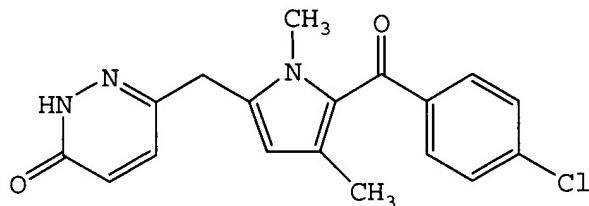
25 7. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 2.

30 8. The method according to claim 7, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-2 IC₅₀ of less than about 0.2 μmol/L and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 100.

9. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-1 IC₅₀ of at least about 1 μmol/L.

10. The method according to claim 9, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a cyclooxygenase-1 IC₅₀ of at least about 10 μmol/L.

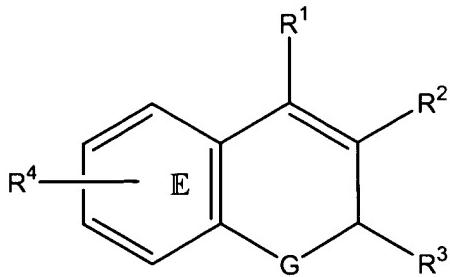
11. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor comprises 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, having the formula:



or a prodrug thereof.

12. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a chromene.

13. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, and dihydronaphthalenes
20 having the general formula:



wherein G is selected from the group consisting of O, S and NR^a;

wherein R^a is alkyl;

5 wherein R¹ is selected from the group consisting of H and aryl;

 wherein R² is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;

 wherein R³ is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

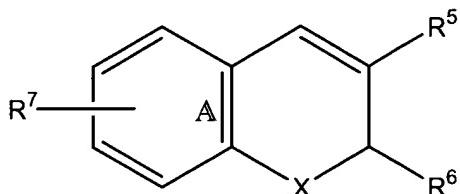
10 wherein R⁴ is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

15 or wherein R⁴ together with ring E forms a naphthyl radical;

 or an isomer thereof; and

 including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

14. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



5

wherein:

X is selected from the group consisting of O, S and NR^b ;

R^b is alkyl;

10 R^5 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;

R^6 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl and each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

15 R^7 is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^7 together with ring A forms a naphthyl radical;

25 or an isomer or prodrug thereof.

15. The method according to claim 14, wherein:

X is selected from the group consisting of oxygen and sulfur;

- R^5 is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;
- R^6 is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and
- 5 R^7 is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl;
- 10 or wherein R^7 together with ring A forms a naphthyl radical; or an isomer or prodrug thereof.
- 15 16. The method according to claim 14, wherein:
- R^5 is carboxyl;
- R^6 is lower haloalkyl; and
- R^7 is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^7 together with ring A forms a naphthyl radical;
- 20 or an isomer or prodrug thereof.
- 25 17. The method according to claim 14, wherein:
- R^6 is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R⁷ is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R² together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

18. The method according to claim 14, wherein:

R⁶ is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R⁷ is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R⁷ together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

19. The method according to claim 14, wherein the cyclooxygenase-2 selective inhibitor comprises:

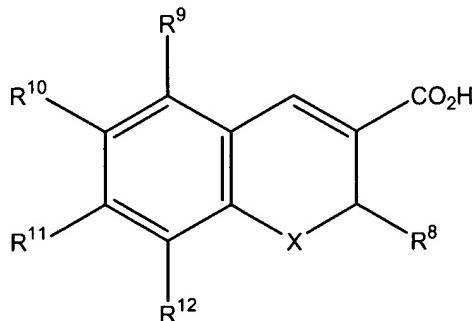
- a) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- b) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- c) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- d) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 e) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- f) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 g) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- h) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- i) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- j) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- k) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 l) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 o) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 r) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- s) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- t) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- u) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;
- 30 v) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- w) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- x) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 y) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- z) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- aa) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 bb) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- cc) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 dd) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- ee) 6-[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- ff) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 gg) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- hh) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 ii) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- jj) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- kk) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
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- II) 8-chloro-6-[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- mm) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 nn) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- oo) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- pp) 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 qq) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- rr) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- ss) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 tt) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid; and
- uu) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
- 20 or a prodrug of such compound.

20. The method according to claim 6, wherein the cyclooxygenase-2 specific inhibitor comprises a compound having the formula:



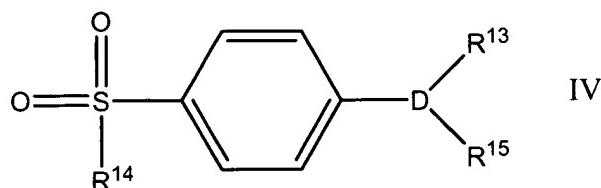
wherein:

- X is selected from the group consisting of O and S;
- R^8 is lower haloalkyl;
- R^9 is selected from the group consisting of hydrido, and halo;
- R^{10} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6-membered nitrogen-containing heterocyclosulfonyl;
- R^{11} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and
- R^{12} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;
- or an isomer or prodrug thereof.
21. The method according to claim 20, wherein:
- R^8 is selected from the group consisting of trifluoromethyl and pentafluoroethyl;
- R^9 is selected from the group consisting of hydrido, chloro, and fluoro;
- R^{10} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;
- R^{11} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and
- R^{12} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;
- or an isomer or prodrug thereof.
22. A method of treating or preventing a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the

subject having or susceptible to said disorder with a therapeutically-effective amount of a combination of a compound or salt of any of the compounds described in any one of claims 6 – 21 and reboxetine.

23. The method according to claim 2, wherein the cyclooxygenase-2 mediated disorder is selected from the group consisting of a CNS disorder, inflammation, arthritis, pain and fever.

24. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a material selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure:



wherein:

D is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R¹³ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R¹³ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

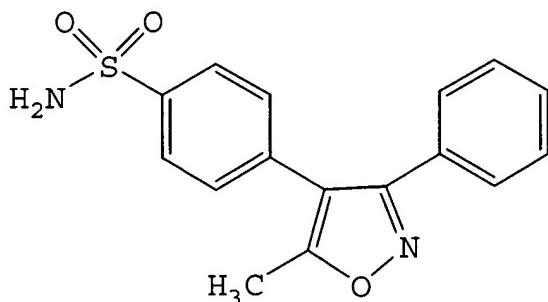
R¹⁴ is selected from the group consisting of methyl and amino; and

R¹⁵ is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl,

haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amine, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylamino sulfonyl, arylsulfonyl, and N-alkyl-N-arylamino sulfonyl;

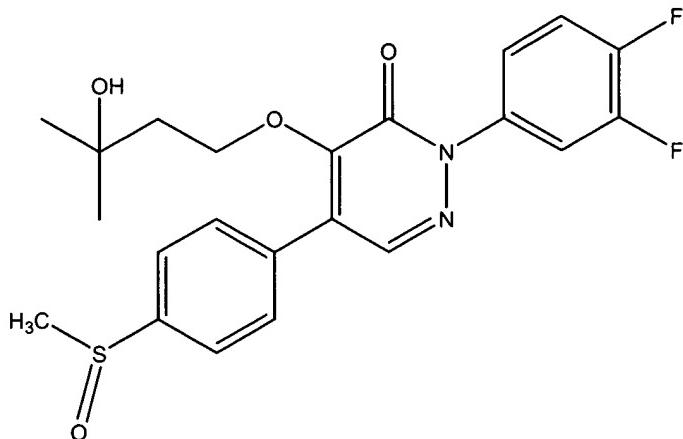
or a prodrug thereof.

25. The method according to claim 1, wherein the
15 cyclooxygenase-2 selective inhibitor comprises valdecoxib, having the
following structure:



20 or a prodrug thereof.

26. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the structure:

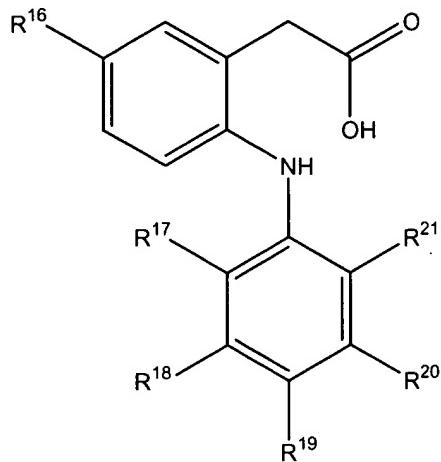


5 or a prodrug thereof.

27. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, JTE-522, deracoxib, a chromene, a chroman, parecoxib, valdecoxib, etoricoxib, rofecoxib, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963, meloxicam, BMS-347070, prodrugs of any of them, and mixtures thereof.

10 28. The method according to claim 27, wherein the cyclooxygenase-2 selective inhibitor comprises celecoxib or a prodrug thereof.

15 29. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a phenylacetic acid derivative represented by the general structure:



wherein R¹⁶ is methyl or ethyl;

R¹⁷ is chloro or fluoro;

5 R¹⁸ is hydrogen or fluoro;

R¹⁹ is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R²⁰ is hydrogen or fluoro; and

R²¹ is chloro, fluoro, trifluoromethyl or methyl,

10 provided that R¹⁷, R¹⁸, R¹⁹ and R²⁰ are not all fluoro when R¹⁶ is ethyl and R¹⁹ is H;

or a prodrug thereof.

30. The method according to claim 29, wherein:

R¹⁶ is ethyl;

15 R¹⁷ and R¹⁹ are chloro;

R¹⁸ and R²⁰ are hydrogen, and

R²¹ is methyl;

or a prodrug thereof.

31. The method according to claim 1, wherein an amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof together with an amount of reboxetine, constitute an amount effective for the treatment, prevention, or inhibition of the CNS disorder, pain and inflammation, or inflammation-associated disorder.

32. The method according to claim 1, wherein the amount of reboxetine is within a range of from about 1 mg/day to about 10 mg/day.

33. The method according to claim 32, wherein the amount of reboxetine is within a range of from about 2 mg/day to about 8 mg/day.

5 34. The method according to claim 33, wherein the amount of reboxetine is within a range of from about 3 mg/day to about 6 mg/day.

10 35. The method according to claim 32, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range of from about 0.01 to about 100 mg/day per kg of body weight of the subject.

36. The method according to claim 35, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range of from about 1 to about 20 mg/day per kg of body weight of the subject.

15 37. The method according to claim 1, wherein the weight ratio of the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof to the amount of reboxetine that is administered to the subject is within a range of from 1:1 to about 1000:1.

20 38. The method according to claim 37, wherein the weight ratio of the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof to the amount of reboxetine that is administered to the subject is within a range of from about 50:1 to about 100:1.

25 39. The method according to claim 1, wherein the pain and inflammation or inflammation-associated disorder is selected from the group consisting of neuropathic pain, headache, fever, arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, 30 gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome,

ulcerative colitis, cancer, colorectal cancer, herpes infections, HIV,
5 pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis,
candidiasis, lumbar spondylanhrosis, vascular diseases, migraine
headaches, sinus headaches, tension headaches, dental pain, periarteritis
nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma,
rheumatic fever, diabetes mellitus (type 1 and type 2), myasthenia gravis,
multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome,
10 polymyositis, gingivitis, hypersensitivity, swelling occurring after injury,
myocardial ischemia, ophthalmic diseases, retinitis, retinopathies,
conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue,
pulmonary inflammation, nervous system disorders, cortical dementias,
and Alzheimer's disease.

15 40. The method according to claim 1, wherein the pain and
inflammation or inflammation-associated disorder is an ophthalmic
disease or ophthalmic injury.

20 41. The method according to claim 40, wherein the ophthalmic
disease or ophthalmic injury is selected from the group consisting of
retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute
injury to the eye tissue.

25 42. The method according to claim 39, wherein the pain and
inflammation or inflammation-associated disorder is arthritis.

43. The method according to claim 42, wherein the arthritis is
osteoarthritis.

25 44. The method according to claim 42, wherein the arthritis is
rheumatoid arthritis.

45. The method according to claim 1, wherein the subject is an
animal.

46. The method according to claim 45, wherein the subject is a
human.

30 47. The method according to claim 2, wherein the
cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine are

administered to the subject enterally or parenterally in one or more dose(s) per day.

48. The method according to claim 47, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine are administered to the subject substantially simultaneously.

5 49. The method according to claim 47, wherein the cyclooxygenase-2 selective inhibitor and reboxetine are administered sequentially.

10 50. The method according to claim 1, wherein the CNS disorder is selected from the group consisting of Alzheimer's disease (AD), amnesia, amyotrophic lateral sclerosis (ALS), anorexia nervosa, anxiety disorder, anxiety neurosis, ataxia, attention deficit hyperactivity disorder, autism, autonomic nervous system disease, behavior disorder, bipolar disorder, brain injury, bulimia, catatonia, central nervous system disease, chronic 15 psychiatric indications, chronic urological indications, incontinence, cognitive disorder, convulsion, cranial neuropathy, cyclothymia or cyclothymic personality, cystocele, delirium, delusional (paranoid) disorders, dementia, depression, diabetic neuropathy, diverticula, dystonia, dystonia, dysuria, eating disorder, encephalitis, epilepsy, 20 extrapyramidal syndrome, feeding disorder, hermaturia, Huntington's disease (HD) or Huntington's chorea, hydronephrosis, hydroureter, hypochondriacal neurosis, hypomanic personality, hypoxia, hysteria, hysterical neurosis, manic depression, meningitis, mental deficiency, mental disorder, motor neurone disease, movement disorder, muscular 25 spasm, multiple sclerosis, myalgia, name, narcissism, nervous system injury, neurodegenerative disease, neurological disease, neurological, mental and cognitive disorder, neuropathy, obsessive/compulsive disorder, obsessive-compulsive neurosis, opiate use disorder, paralysis, Parkinson's disease (PD), passive-aggressive disorder, personality disorder, phobic neurosis, pneumaturia, posttraumatic stress disorder, psychopathy, psychosis, schizophrenia, seizure, senile dementia, sleep 30

disorder, sociopathy, somatization disorder, stupor, substance dependence, tardive dyskinesia, and tinnitus.

5 51. A method for the treatment, prevention, or inhibition of a disorder in a subject, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine to the subject, wherein the disorder is selected from the group consisting of actinomycosis, acute appendicitis, acute cholecystitis, acute hemorrhagic encephalitis, acute hepatitis, acute injury to the eye tissue, acute myocardial infarction, acute pancreatitis, adenitis, amebiasis, amebic colitis, anal fissures, ankylosing spondylitis, aphthous stomatitis, aphthous ulcers, aplastic anemia, appendiceal abscess, arachnoiditis, arteritis, arthritis, asthma, atherosclerosis, atopic dermatitis, B virus myelitis, "backwash" ileitis of ulcerative colitis, bacterial endocarditis, Behcet's syndrome, berylliosis, blastomyces dermatitidis, blepharitis, brain abscess, bronchiectasis, 10 bronchiolitis, brucellosis, bursitis, cancer and associated pain, candidiasis, carcinoma of the bile ducts, cat-scratch fever, cavernous sinus thrombosis, cecal diverticulitis, cellulitis, cerebral epidural abcess, cholelithiasis, chondritis, choreoretinitis, chronic active hepatitis, chronic urological indications, incontinence, coccidioides immitis, colorectal cancer, 15 conjunctivitis, cortical dementias, cortical thrombophlebitis, Crohn's disease, cryptococcus neoformans, cystic fibrosis, dacryocystitis, dental pain, dermatomyositis, diabetes mellitus (type 1 and type 2), diabetic neuropathy, diverticula, dysuria, encephalitis, encephalomyelitis, endometritis, endophthalmitis, eosinophilic gastroenteritis, epicondylitis, 20 epiglottitis, erythema multiforme, erythema nodosum, external ear inflammatory disease, fasciitis, fibromyalgia, fistulas, folliculitis, gastric ulcer, gastric varices, gastritis, gingivitis, gliosis, glomerulonephritis, gonococcal infection, gout, granulomatous colitis, hemorrhoids, hepatitis, hermaturia, herpes, HIV1, Hodgkin's disease, hypersensitivity, ileal carcinoid, ileitis, 25 ileocecal tuberculosis, ileocolitis, ileojejunitis, iliofemoral venous thrombosis, incarcerated hernia, infarction of the colon, inflammatory bowel disease, 30

interstitial keratitis, intestinal obstruction, iritis, irritable bowel syndrome, ischemia, ischemic colitis, kidney stones, labyrinthitis, lateral sinus thrombosis, leprosy, low back pain, lumbar spondylolisthesis, lymphadenitis, lymphangitis, lymphogranuloma inguinale, lymphosarcoma, mastoiditis, mesenteric thrombosis, metastatic melanocarcinoma, migraine headache, minor injuries, multiple sclerosis, myasthenia gravis, myocardial ischemia, myositis, myringitis, nephritis, nephrotic syndrome, neuritis, neuronitis, neuropathic pain, neurosyphilis, nodular lymphoid hyperplasia, ocular photophobia, ocular photophobia, ophthalmic diseases, osteoarthritis, osteomyelitis, otitis, ovarian carcinoma, panencephalitis, papillitis, parenchymatous, pelvic inflammatory disease, perforated ulcer, perianal abscess, periarteritis nodosa, pericarditis, pericholangitis, periodontitis, peritonitis, pharyngitis, pleuritis, pneumaturia, pneumonia, pneumonitis, poliomyelitis, polymyositis, postherpetic neuralgia, prostatitis, pseudomembranous enterocolitis, pseudopolyps, psoriasis, pulmonary edema, pulmonary infarction, pulmonary inflammation, pulpitis, pyelonephritis, pylephlebitis, pyoderma gangrenosum, rabies, radiation colitis, radiation enteritis, rectal prolapse, regional enteritis, renal amyloidosis, retinitis, retinopathies, rheumatic fever, rheumatoid arthritis, rhinitis, rickettsiae, sacroiliitis, salpingitis, sarcoidosis, scleritis, sclerodema, sclerosing cholangitis, septic thrombophlebitis, shigellosis, shingles, sinus headaches, sinusitis, spinal epidural abscess, splenitis, subdural empyema, swelling occurring after injury, syphilitic meningo-vascular syphilis, tabes dorsalis, tendonitis, tenosynovitis, tension headaches, thyroiditis, tonsillitis, toxic megacolon, transverse myelitis, trigeminal neuralgia, tuberculosis enteritis, typhoid fever, ulcerative colitis, ulcerative proctitis, ureteritis, uveitis, vaginitis, vascular diseases, vascular necrosis, vasculitis, ventricular empyema, vestibulitis, viral infections, wound healing, and Zollinger-Ellison syndrome.

30 52. A method for the treatment or prevention of a disorder having an inflammatory component in a subject in need of said treatment

or prevention of disorders having an inflammatory component, the method comprising the step of administering to the subject a therapeutically effective dose of a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof and reboxetine.

5 53. A composition for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine.

10 54. The composition according to claim 53, wherein the composition is useful for treating a subject in need of treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder, and wherein a dose of the composition constitutes an amount of a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof and an amount of reboxetine that together constitute a CNS disorder, pain and inflammation, or inflammation-associated disorder suppressing treatment, prevention, or inhibition effective amount.

15 55. The composition according to claim 53; wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine are present in a combination of the cyclooxygenase-2 selective inhibitor and reboxetine as described in any one of claims 3 - 29 and 24 - 38.

20 55. A pharmaceutical composition comprising a cyclooxygenase-2 specific inhibitor or prodrug thereof; reboxetine; and a pharmaceutically-acceptable excipient.

25 56. The pharmaceutical composition according to claim 55, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine are present in a combination of the cyclooxygenase-2 selective inhibitor or prodrug thereof and reboxetine as described in any one of claims 3 - 29 and 24 - 38.

30 57. A kit that is suitable for use in the treatment, prevention or inhibition of a CNS disorder, pain and inflammation or inflammation-

associated disorder, the kit comprises a first dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof and a second dosage form comprising reboxetine, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder.